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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,989	07/28/2006	Michael David Barker	PB60708	4223

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KING OF PRUSSIA, PA 19406-0939

EXAMINER	
O DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
05/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/587,989	BARKER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12,13 and 15-25* is/are pending in the application.

4a) Of the above claim(s) *13 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,12 and 16-25* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/2010; 07/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-10, 12, 13 and 15-25 are pending in the current application.

2. This application is a 371 of PCT/GB05/00274 filed 01/27/2005 which claims priority to UNITED KINGDOM 0402137.4 filed 01/30/2004.

Response to Restriction Election

3. Applicant's election of Group I and the species (Example 1: [N-Cyclopropyl-4-methyl-3-{1-[(1-methylethyl)sulfonyl]lH-pyrazolo[3,4-c]pyridin-5-yl}benzamide) in the reply filed on January 18, 2010 is acknowledged. The election of an intended use of chronic obstructive pulmonary disorder in the response of April 6, 2010 is acknowledged. No explanation of which claims read on the elected species was made, however it appears that of the new claims, all but claim 22 reads on the new claims. The failure to state which claims read on the elected species can be held non-responsive (See page 7 of the Restriction Requirement), however in order to advance prosecution the examiner has determined all the new claims save claim 22 read on the species. Regardless the species is allowable and the examination extended to the whole compound group.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is an omnibus type claim. The phrase "substantially as hereinbefore defined" makes it unclear what is in the claim. Moreover a claim to "Examples 1 to 58" should

be stated either by names or formulae. This reliance on the specification does not comply with 112 2nd paragraph. See *Ex Parte Fressola* 27 USPQ2d 1608:

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. Claims in utility applications [1] that define the invention entirely by reference to the specification and/or drawings, so-called "omnibus" or "formal" claims, while perhaps once accepted in American patent practice, are properly rejected under Section 112 Para. 2 as failing to particularly point out and distinctly claim the invention. See MPEP Section 706.03(h) (5th ed., rev. 14, Nov. 1992); Landis, Mechanics of Patent Claim Drafting, Section 2 (1974). This analysis is limited to claims in utility applications. Plant patent claims are defined "in formal terms to the plant shown and described." Claims in design patents are recited in formal terms to the ornamental design "as shown" or, where there is a properly included special description of the design, the ornamental design "as shown and described." MPEP Section 1503.01.....The general rule is that the claims should be self-contained; that is, they should not expressly rely upon the description or drawing to give them meaning. . . . The terms "substantially as described" and the like, once much used in claims (GLASCOCK 1943 Section 5640) are now rarely seen. The Office disregards them in interpreting claims. . . . Claims consisting only in a reference to the disclosure, as "The features of novelty herein disclosed," are not allowed except in design cases.....A claim which refers to the specification defeats the purpose of a claim."

5. Claim 25 recites the limitation "wherein the condition or disease....." in claim 1 there is no disease. Even in claim 25 there is no disease either, such that the claim makes no sense grammatically. There is insufficient antecedent basis for this limitation in the claim. Claim 25 also recites "derivative". It is unclear what derivation is being applied to arrive at said derivative so the scope of this claim is unclear. It also fails to further limit the parent claim. It is noted that claim 1 has been amended to replace salt for derivative, which is acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The claims are extremely broad encompassing an unknown list of diseases, described only as "a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase." a partial list is on page 28: "rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis,

aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome, inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer." Cancers appear to be incompletely listed but also include others not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma,

adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis;

and Adrenal glands: neuroblastoma. Thus, the scope is broad. The elected intended use is chronic obstructive pulmonary disease.

(B) This is a compound invention but it requires use of the intended use of treatment of diseases and disorders described in the following way: "a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase." This claim is ostensibly being evaluated as a method claim.

(D) One of ordinary skill is a medical doctor.

(C) (E) The existence of a "silver bullet" for all these diseases is contrary to our present understanding of pharmacology and medicine. According to van den Blink et. al. "p38 Mitogen-Activated Protein Kinase Inhibition Increases Cytokine Release by Macrophages In Vitro and During Infection In Vivo" Journal of Immunology 2001, 166, 582-587, interest in p38 MAPK inhibition is related to inflammation, however "the exact function of p38 MAPK in inflammation remains ambiguous" and that "The most marked effect of p38 MAPK inhibition is the altered control of cytokine release." Presumably to treat inflammation the compounds would need to inhibit cytokine release, however Blink shows that p38 MAPK cytokine release is highly dependent on cell type. "As p38 MAPK has been suggested to be a suitable target for in vivo anti-cytokine therapy in a number of inflammatory diseases, the possible cell type-specific effects of p38 MAPK inhibition make it important to assess the action of p38 MAPK inhibition on cytokine production during pathophysiology in vivo." "The most puzzling finding in the present study is the apparent cell-specific effect of p38 MAPK inhibition on cytokine release, enhancing cytokine production in peritoneal macrophages and a macrophage cell line but inhibiting this production in other cell types and whole blood." Conclusion

The instant claims embrace many unrelated diseases with distinct etiologies and different treatments including cancer. For a discussion of cancer treatment see Simone, Oncology: Introduction, *Cecil Textbook of Medicine*, 20th Edition, 1996 Vol. 1, pp. 1004-1010, states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study' (see page 1004). A tumor is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Different types of tumors affect different organs and have different methods of growth and harm to the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all solid tumors. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). Dosage regimen is dependent on several risk factors. See Trisha Gura "CANCER MODELS: Systems for Identifying New Drugs Are Often Faulty" Science 7 November 1997: Vol. 278. no. 5340, pp. 1041 - 1042:

"Indeed, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration. "**The fundamental problem in drug discovery for cancer is that the model systems are not**

predictive at all," says Alan Oliff, executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania."

There is not even a basic causal link between many of the diseases listed and the pathway claimed. In the field of MAPK immunology, it is known that JNK, not p38, is associated with neurodegenerative disease.

(F) In the instant case we have been given very limited information as to what these compounds are doing in the pharmacological sense. The only information in the specification is a reference to performance in a test tube assay for inhibiting a p38 MAPK enzyme.

(G) The application has provided no working examples of the treatment of any disease. The clinical benefit of any p38 kinase inhibitor in the diseases mentioned above has never been demonstrated.

(H) Presumably to use this invention one would need to make all the compounds of claim 1 and test them against all the various diseases in animals or humans. It is not at all clear what these compounds would do inside an organism. Based on the teaching of Blink the complexity of p38 kinase signaling precludes conclusions based solely on enzyme inhibition alone. The instant claims in their narrowest embodiment, inflammation and the elected species of COPD, are not enabled and that cytokines would be released by some cells in the organism. It is clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation.

7. Claims 1-2, 3-8, 10, 12, 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein A is susbtituted by -(CH_2)q-aryl, amides, sulfonamides, amines and other small groups i.e. alkyl, halogen, cyano (something like claim 3, where the nesting is limited) and where R11 and R12 are alkyl, cycloalkyl, and pyrazole

it does not reasonably provide enablement for compounds where A is (CH2)n-heterocyclyl, or other various prophetic nested variables, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a plethora of matryoshka prophetic variables.

(B) The nature of the invention: This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as kinase inhibitors.

(D) The level of one of ordinary skill: One of ordinary skill is an organic/medicinal chemist.

(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

Only a few examples were made and they are relatively homogenous. The R11/R12 variable is only ever a few groups. The only real variation is on the groups on the A ring. The A-ring only

has two positions available for substiutents so it is unclear how A can have all of these groups, up to 3.

While some compounds outside those exemplified might be prepared by a skilled artisan, the paucity of working examples point to the key deficit in the disclosure, namely that the "how to use" requirement of 112 1st paragraph has not been met. While organic chemistry is highly unpredictable, the degree of unpredictability in the kinase inhibitor development art is even greater. The instant claims are drawn to an enormously broad recitation of prophetic moieties. The specification makes only the following statements about how compounds perform in the various kinase inhibition assays.

Results

The compounds described in the Examples were tested in at least one of the assays described above and had either IC_{50} values of <10 μM or pK_i values of >6.

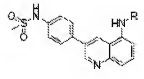
The medicinal chemistry of kinases is relatively well-developed and many limitations are well known in the art. The use of compounds as kinase inhibitors is highly dependent upon the structure of the compounds. These compounds are sensitive to structural changes that may be relatively minor in the chemical sense see, Michelotti et. al. "Two classes of p38a MAP kinase inhibitors having a common diphenylether core but exhibiting divergent binding modes" *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 5274-5279: "In compounds of Series 2, addition of a 4-fluoro group (compound 2a) (Fig. 2) to the diphenylether results in a 2- to 3-fold increase in potency, while substituents in the 2 and 3 positions appear to be unfavorable. Removal of the phenol hydroxyl of compound 2c results in a significant loss in activity (compound 2f), suggesting that this substituent plays an important role in binding. **Modification**

of the sulfamide linker of compound 2c to a sulfonamide linker (compound 2h) results in a complete loss of measurable activity."

In the instant case, very few details of regarding the choice of substituents required for activity has been given. The state of the art in the development of kinase inhibitors is highly unpredictable, See Jiang et. al. "3,5-Disubstituted quinolines as novel c-Jun N-terminal kinase inhibitors." *Bioorganic & Medicinal Chemistry Letters* **2007**, *17,* 6378-6382, where very small changes such as the removal of a halogen atom, or the position of a pyridine led to inactive compounds. Compare compounds 10c-10i to compounds 13a-13c. In the words of Jiang:

"It was surprising that the **13a** was completely inactive versus JNK3, whereas the 3- and 4-pyridyl analogs (**13b** and **13c**), though slightly better, were still considerably less active than the N-linked analogs 10a-i."

For convenience a portion is shown below:



10

Table 2. Inhibition of JNK3 by phenanthroline derivatives 10

Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
10a		0.44 ± 0.09	>20
10b		0.48 ± 0.06	>20
10c		3.6 ± 0.32	nt
10d		0.76 ± 0.15	nt
10e		15 ± 0.17	nt
10f		6.5 ± 0.53	nt
10g		0.12 ± 0.02	>20
10h		0.14 ± 0.02	nt
10i		0.49 ± 0.06	nt

[a] Values are means of three experiments; nt, not tested.

Table 3. Inhibition of JNK3 by pyridyl derivatives 13

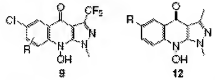
Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
13a		>20	nt
13b		5.2 ± 0.39	>20
13c		5.0 ± 0.37	>20

[a] Values are means of three experiments, nt, not tested.

See also Liu et. al. "Synthesis and SAR of 1,9-dihydro-9-hydroxypyrazolo[3,4-b]quinolin-4-ones as novel, selective c-Jun N-terminal kinase inhibitors" *Bioorganic & Medicinal Chemistry*

Letters **2006**, *16*, 2590-2594. "Analog 12a, in which chlorine was replaced with hydrogen, was not active against JNK1, whereas there was only a slight decrease in activity when chloride was replaced with bromide (10). However, replacement of chlorine by an aryl group at the same position gave only inactive compounds (12b,c). Most analogs (9a-9d) with substitution at the 5, 7, and 8 positions of the ring were inactive as well."

Table 1. Enzymatic and cellular activity of analogs with aromatic ring modifications



9

12

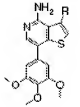
Compound	R	JNK1 IC_{50} (μM)	Pc-Jun IC_{50} (μM)
1	.....	1.22	>30
2	.....	0.98	16.4
10	.....	0.92	>30
9a	5-Cl	>10	NT[a]
9b	7-Cl	5.14	>30
9c	8-OMe	>10	NT[a]
9d	7-$N(Me)_2$	>10	NT[a]
12a	H	>10	NT[a]
12b	Ph	>10	NT[a]
12c	1*H*-Pyrazol-3-yl	>10	NT[a]

[a] Compounds with enzymatic IC_{50}'s greater than 10 μM were not tested in the cellular assay.

By changing the structure of the compound a conformational shift occurs, and rather unremarkably the ability of the compound to interact with its target is gone. See also, Miyazaki et. al. "Design and effective synthesis of novel templates, 3,7-diphenyl-4- amino-thieno and furo-[3,2-c]pyridines as protein kinase inhibitors and in vitro evaluation targeting angiogenetic kinases" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 250–254, state:

"As the data indicate, compounds with hydrophobic chloro groups regardless of substitution position (6d, 6e, and 6j) show submicromolar inhibitory activity. However, those with somewhat hydrophilic substituents such as 3-acetamido, 4-acetyl, and 4-methylsulfonyl groups (6f, 6g, and 6i) are relatively inactive. Other substituents such as 4-methoxyphenyl, naphthyl, and pyridyl provided analogues with moderate potency (6b, 6c, and 6h). The need for a phenyl group for inhibitory activity is evidenced by the lack of activity of 6a."

Table 1. EphB4 kinase enzyme inhibition of 4-amino-3-aryl-7-(3,4,5-trimethoxylphenyl)-thieno[3,2,c]pyridines 6



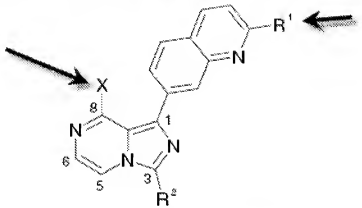
Compound	R	EphB4 IC_{50} (nM)
6a	Br	>25,000
6b	4-OMe-phenyl	7100
6c	β-Naphthyl	2200
6d	4-Cl-phenyl	190
6e	3-Cl-4-*F*-phenyl	110
6f	3-acetamide-phenyl	>25,000
6g	4-Acetyl-phenyl	>25,000
6h	3-Pyridyl	3900
6i	4-Methylsulfonyl-phenyl	>23,000
6j	2,3-Dichloro-phenyl	230

The structure activity relationships of kinase inhibitor pharmacophores have been discussed in Mulvihill et. al. "Novel 2-phenylquinolin-7-yl-derived imidazo[1,5-a]pyrazines as potent insulin-like growth factor-I receptor (IGF-IR) inhibitors" *Bioorganic & Medicinal Chemistry* **2008**, *16*, 1359–1375.

"To confirm the key pharmacophores and to test the binding model, we removed the terminal phenyl ring, replaced the cyclobutyl ring with a smaller methyl group, and also replaced the 8-amino group with a hydroxyl group, synthesizing three key compounds, 2b–c and 9, respectively. Based on the binding model, the space occupied by the terminal phenyl cannot be fully occupied by hydrophobic collapse of the nearby residues, suggesting compound 2b should

be inactive.....**It was evident that the terminal phenyl ring as well as the 8-amino group, as exemplified by compounds 2b and 9, respectively, were both vital pharmacophores required for IGF-IR inhibition.** Truncation of the cyclobutyl moiety to methyl (compound 2a ! 2c) afforded a 12-fold loss in potency, highlighting that critical mass was required at the C3-position of the imidazopyrazine ring for significant IGF-IR inhibition. These data reinforced previous SAR findings from the benzyloxyphenyl series and indicates that multiple atoms in the ring make non-specific contacts with the protein."

Table 1. 3T3/huIGF1R IC_{50} values for compounds **1**, **2a–c**, and **9**



Compound	X	R^1	R^2	IGF-IR cell IC_{50} (μM)
1	----	----	----	1.16
2a	NH_2	Ph	Cyclobutyl	0.086
2b	NH_2	H	Cyclobutyl	>10.0
2c	NH_2	Ph	Methyl	1.04
9	OH	Ph	Cyclobutyl	>10.0

The same author shown that for this pharmacophore, the activity is governed by the interaction of the compound with key residues of the IGF-IR protein. Mulvihill et. al. "1,3-Disubstituted-imidazo[1,5-a]pyrazines as insulin-like growth-factor-I receptor (IGF-IR) inhibitors" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 1091–1097.

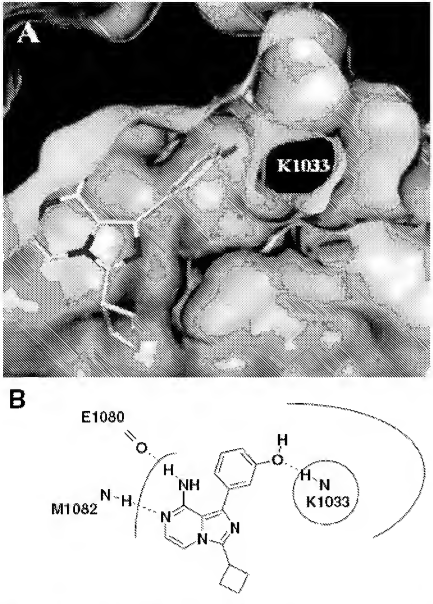


Figure 2. (A) Surface display of a model of the ATP binding pocket with compound 6a.6 bound. The surface is colored by depth from shallow/solvent-exposed blue to deeply buried orange. The hole in the surface is the space carved out by K1033. A small space 'behind' K1033 is visible. (B) 2D representation of Figure 2A, highlighting the key interactions in the site. The basic amine of K1033 makes a key hydrogen bond with the hydroxyl. Canonical hinge binding interactions are also present.

Kinase active sites are highly conserved amino acid sequences across several classes. The compounds are generally mimics of the natural enzyme substrate ATP, such that a compound that is too large and has all of these prophetic groups hanging off of it simply won't fit into the enzyme active site or allow for the very subtle interactions required for inhibition. In this case the prepared compounds bear a structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only four working examples in this unpredictable art without undue experimentation.

Objections

8. Claim 9 is objected to for depending from a rejected base claim, but would be allowable if put in proper independent form.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JANET ANDRES can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/David K. O'Dell/
Examiner, Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625